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ASSOCIATE VICE PRESIDENT
CLINICAL AFFAIRS

PhRMA

August 31, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5636 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. **99D-1541** - Draft Guidance for Industry on Establishing Pregnancy Registries (64 Federal Register 30041 (June 4, 1999)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invest over $24 billion annually in the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the use of pregnancy registries as a specific research methodology in specific circumstances. We appreciate the opportunity to provide comments on the Draft Guidance for Industry on Establishing Pregnancy Registries (Federal , *Register* **64**: 30041, June 4, 1999).

PhRMA supports FDA in its efforts to provide consistent guidance to industry regarding pregnancy registries. This methodology is not widely understood or consistently implemented, and such guidance has the potential to greatly enhance the validity and utility of data emanating from these registries, in addition to minimizing confusion regarding the regulatory status of reports of adverse events arising from pregnancy registries. While the draft guidance document is a good beginning, there are a number of areas in the document which PhRMA thinks could be enhanced. We have provided comments on the document in general, as well as comments to each section of the document.

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Major Points of PhRMA's Comments

The three most important aspects of PhRMA's comments on this draft guidance document are to encourage FDA to provide:

1. A clear and concise standard definition of a pregnancy registry, perhaps including a discussion of how a registry differs from standard clinical trials and other epidemiologic methods, such as case-control studies;
2. A statement of the scientific and regulatory objectives of pregnancy registries, including clear guidance on when a pregnancy registry is needed and the types of information which can be expected to be generated by a pregnancy registry;
3. A clear discussion of regulatory reporting requirements for adverse event reports arising from pregnancy registries, and the rationale for these requirements.

With respect to the first item, the draft guidance document does not provide a standard definition of a pregnancy registry, although it does seem clear that two key features of a registry are that it must be **prospective** in nature and it must include **active** collection of data. However, the document seems to alternatively describe a pregnancy registry as a system to collect information on specific drug/biologic exposures, and as a cohort study that enrolls women exposed to a certain product during pregnancy and a comparative non-exposed cohort. Similarly, the difference in design between an active surveillance program (i.e., a registry) for signal detection and hypothesis generating, and a study for hypothesis testing is blurred in the guidance document. The impression given is that concurrent comparison groups are always necessary. Registries typically do not have concurrent internal comparison groups; comparisons are usually to external rates. Although theoretically it might be desirable to have a comparative cohort enrolled at the same time, the selection of this comparative cohort requires a great deal of planning, and sufficient information about the hypotheses to be tested may not be available at the inception of the registry. Certainly, even non-comparative registries can be used for hypothesis testing as well, using nested case-control designs, for example.

With respect to the scientific objectives of pregnancy registries, it is not clear whether FDA's view is that historical registries have demonstrated their value primarily in (1) detection of a new safety signal during pregnancy or in (2) quantifying the frequency of observation of a known adverse event during pregnancy. Clarification of these or other scientific objectives (with examples from previous registries) are, in PhRMA's view, essential to this guidance.

The draft guidance is totally silent with respect to the regulatory objectives of pregnancy registries. Yet, both FDA and regulated industry recognize that it is essential to know whether an objective of collecting information in a pregnancy registry is to support product-specific labeling on use of the drug in pregnant women. PhRMA urges FDA to address this topic. Importantly, PhRMA also encourages FDA to provide examples since, to our knowledge, very few pregnancy registries have resulted in drug information that was deemed useful in prescription drug labeling. In fact, among currently approved prescription drug products, we are only aware of information from a pregnancy registry being included in labeling for one product (i.e., Zovirax® Capsules). Importantly, in this case, the labeling states that the data collected in the registry do not permit definitive conclusions. This single experience in the public domain of labeling suggests that registries have, historically, had no substantial yield with regard to product labeling. The draft guidance should address this issue since the tone of the draft guidance is quite clearly directed toward encouraging sponsors to initiate registries, although the outcome of such an effort is not clear.

Recognizing that information on the scientific and regulatory objectives of pregnancy registries should be forthcoming in the next version of the guidance, PhRMA urges FDA to recognize the relatively limited experience with pregnancy registries. in view of this limited experience, there may be substantial merit to FDA and industry specifically tracking the yield of pregnancy registries, using specific metrics.

With respect to the third point above, FDA has not addressed by regulation the reporting of adverse events from pregnancy registries, and FDA's guidance to various sponsors has been inconsistent. Guidance is definitely needed in this area; however, the draft document does more to add to the confusion than to ameliorate it. On one hand, FDA states that pregnancy registries are post-marketing studies; while on the other hand, they state that adverse events reported in these registries should be treated as spontaneous reports. These reports are definitely not spontaneous in nature, and we fail to understand FDA's rationale for requiring reporting as if they were. The draft guidance also mentions that sponsors may seek waivers from these reporting requirements if they so desire. This approach will lead only to more inconsistency and confusion.

As an active surveillance program, a pregnancy registry is not strictly speaking a "postmarketing study" unless it is structured specifically to evaluate an a *priori* hypothesis; nor are reports generated from a registry "spontaneous." We strongly recommend that FDA consider these reports to be solicited reports, as

outlined in FDA's "Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Clarification of What to Report", August 1997, pages 3-4. Under this guidance, solicited reports are to be reported as information obtained from a postmarketing study, and submitted to FDA only if they involve serious, unexpected events for which the sponsor concludes that there is a reasonable possibility that the drug caused the event.

Procedural Comment

FDA's notice in the Federal Register stated that this draft guidance would be the subject of discussion on June 3, 1999 at a public meeting of a Subcommittee of the FDA Advisory Committee for Reproductive Health Drugs. Unfortunately, this draft guidance was not published in the Federal Register until after the public hearing. PhRMA believes that some of its member companies would have made productive use of the opportunity to read this draft guidance prior to the public meeting. However, companies were deprived of this background information and were deprived of the opportunity to comment publicly on aspects of this draft guidance. For the future, PhRMA encourages FDA to publish draft guidance documents sufficiently in advance of a planned public hearing to facilitate informed comment at the hearing.

General Comments on the Draft Guidance Document

As mentioned above, the document should contain a clear and concise definition of a pregnancy registry.

It also needs to be made clear in the guidance document that each pregnancy registry must have clear objectives, which should be outlined in the protocol. A single registry cannot answer all questions regarding use of a drug prior to or during pregnancy (e.g., fertility, fecundity, maternal events, pregnancy outcomes, long-term effects in offspring, etc.). If FDA asks a sponsor to establish a registry to gather additional information to evaluate a specific signal seen in pre-marketing data, then data collection can be so directed. Also, any requirement for pregnancy registries should not have retrospective application to approved products, including those products for which new formulations are being introduced or where efficacy supplements or other requests for labeling changes are under consideration.

Many sections of the document (e.g., Patient Follow-up, Study Outcomes, etc.) begin by stating the minimum information that should be collected, activities that

should be undertaken, etc., and later mention that these things may differ in various registries, depending on the drug, condition, etc. This can be misleading, especially when the beginning statements are taken out of context. It is preferable that the statements regarding variability be stressed, with examples identified as items which should be considered for inclusion in the registry, not items that should be included 'in the registry.

PhRMA encourages FDA to view this draft guidance from an international perspective. Increasingly, many of the pregnancy registries that exist in the United States are, in fact, international in scope. Therefore, it is essential that future new registries be consistent with non-US national and international regulatory/scientific initiatives. Such an approach will facilitate efficient data collection, which in turn will lead to useful conclusions. The document should include consideration of international aspects of pregnancy registries in providing guidance regarding methods, information to be collected, etc., and possible impact on ability to pool data for analysis.

Finally, there may be international interests concerning pregnancy registries within (or outside) of the three ICH regions that should be considered before FDA finalizes this draft guidance; in our opinion, FDA should not make a unilateral decision on this topic that will lead to regulatory divergence.

Comments on Specific Sections of the Draft Guidance Document

I. INTRODUCTION

A statement in this section mentions that pregnancy "registries can provide useful information that can be included in product labeling." This statement presents a fundamental premise underlying this draft guidance. Therefore, it is important to examine this premise. While it is certainly possible that registries can provide useful information regarding potential risks and negative findings, as well as positive findings and reassurance, to the best of our. knowledge, no pregnancy registry has provided useful information for inclusion in product labeling. This record of historical pregnancy registries is important and immediately relevant to the subject of this draft guidance. PhRMA believes that it is essential to review the historical record before FDA moves this draft guidance further toward finalization. Since historical pregnancy registries for FDA-approved drug products are a matter of public record, PhRMA encourages FDA to prepare a simple table of the specific drugs and yield in labeling to date, then incorporate this table as an appendix to the next draft of this guidance.

Also in the first paragraph, FDA states a second fundamental premise of this draft guidance, i.e., "the guidance focuses on establishing a registry to assess suspected or unknown risks to pregnancy outcomes.' This apparently simple statement is actually quite complex in that it encompasses two different goals: (1) assessing suspected risks to pregnancy outcomes and (2) assessing unknown risks to pregnancy outcomes. From PhRMA's perspective, the guidance document should focus solely on the potential utility of pregnancy registries for assessing suspected risks to pregnancy outcomes. Such a focus is, in our view, entirely consistent with FDA's historical practice of requesting that a sponsor voluntarily initiate a pregnancy registry for a new drug with nonclinical toxicologicalor clinical evidence of a substantial risk of adverse impact on pregnancy outcomes. Examples of such new drugs are acyciovir and nucleoside anaiogue antiretroviral drugs. in contrast, there is little justification for incorporating compounds with unknown risk into this draft guidance when there is no substantial risk suggested by results of nonclinical or clinical studies. Such an unnecessarily broad scope would be burdensome and there-is no basis to expect useful information as the outcome. Therefore, PhRMA urges FDA to revise this draft guidance to focus on establishing a pregnancy registry for drugs with suspected risks to pregnancy outcomes.

We agree with FDA's statement in this section that pregnancy registries are not appropriate for known teratogens. However, a statement later in the document (Background, third paragraph) indicates that the registry model may be used to estimate the risk of products known to adversely affect pregnancy outcomes on the developing fetus. These statements appear to contradict each other, and must be clarified.

II. BACKGROUND

in the first paragraph, in the discussion of women who become pregnant during a clinical trial, the draft guidance states, "…if pregnancy occurs during a trial, the usual procedure is to discontinue treatment and-drop the patient from the study." To be complete, this discussion should also indicate that these women, although no longer actively participating in the trial, are followed to determine the outcomes of their pregnancies.

Also in the first paragraph, the draft guidance states that FDA may ask the sponsor of an approvabie product to conduct a pregnancy registry as part of a Phase IV commitment. If approval of a new product hinges on whether or not the sponsor agrees to establish such a registry, it seems that FDA is making this a requirement for approval, not a request. This section also mentions

information obtain&from pregnancy registries being added to product labeling. As mentioned above, PhRMA is not aware that any pregnancy registry to date has provided useful information for inclusion in product labeling. In fact, since registries are primarily signal detection and hypothesis-generating tools, not hypothesis-testing studies, PhRMA wonders if any registry, no matter how well designed, will be able to provide adequate'data to'include in product labeling.

The description of epidemiology and surveillance studies could be clearer.

The third paragraph in this section states that a registry may be used to identify and quantify long-term effects such as delayed development, other neurological impairments, etc. The need for long-term follow-up, subsequent large loss to follow-up, and need for precise instruments for outcome ascertainment make the registry setting inappropriate for identifying and quantifying long-term outcomes. FDA must remember that a registry is an observational tool, not an interventional study. A registry can serve as a source of information on selected patients, for whom additional information can be gathered in a separate data collection exercise, with a specific protocol, as a study (assuming patient consent is obtained, etc.).

III. PREGNANCY REGISTRIES

This section mentions that ". . . Registries should be designed.. . with an expected timeframe.. ." It is often extremely difficult to predict timeframes for completion of a registry. It may be more appropriate to base registry completion on reaching a specific sample size which would provide ability to estimate risk at a certain specified level. This can be determined using statistical power calculations.

The comment regarding a comparison group in the third paragraph is imprecise. For example, is it referring to an internal comparison group, or an external (e.g., historical) comparison group? The language should be revised to express FDA's intent.

IV. WHEN IS A PREGNANCY REGISTRY NEEDED?

Although the first paragraph in this section states that "The evaluation of the need for a registry should take into account the actual or expected use of the product in women of childbearing potential and the perceived level of risk based on animal studies or prior information on the subject or similar products," the second paragraph states that registries are particularly important for products with a "high use pattern in women of childbearing age," including anti-infective

agents, antidepressants, anti-epileptics, and anti-asthmatics. In addition, the bull&points include "any product expected to be used commonly by women of reproductive potential (i.e., especially new molecular entities)." These statements appear to include almost every new pharmaceutical product approved by FDA, and completely ignore the focus on products that have a suspected risk to pregnancy outcomes based on animal studies or previous clinical data. As stated earlier, PhRMA and its member companies strongly object to this approach, since pregnancy registries should be reserved for those products where there is a suspected risk to pregnancy outcomes. For example, consideration of establishing pregnancy registries could be limited to those products with a finding of "significant concern" from application of the recently proposed preclinical data integration tool (Docket 99N-2079, Draft Guidance for Industry on Establishing Pregnancy Registries).

V. WHEN SHOULD A REGISTRY BE ESTABLISHED?

The first paragraph of this section states that a pregnancy registry should be established as early as possible after a new product is deemed approvable. This is not an appropriate timeframe for initiating a pregnancy registry, for a number of reasons. First, it is not universally applicable since many products progress directly to approval without a prior approvable decision. Second, it is not routinely feasible for a sponsor to invest the resources to open a registry prior to approval, and since the product is not yet available for use, there would be no exposed pregnant women to enroll in the registry at this stage. Third, in our view, FDA does not have statutory authority to require initiation of a pregnancy registry at the time of approvable status. However, we do think that in situations where FDA's scientists believe a pregnancy registry may be warranted, FDA should initiate discussions with the sponsor as early as possible, and not wait until the product is approvable. PhRMA believes that such notification would typically occur after the results of reproductive toxicology studies, mutagenicity studies, and Phase II clinical studies are available for review. This schedule would allow sufficient time for discussion with the sponsor and, as appropriate, sufficient time for adequate preparation to open &registry. Perhaps this is a typographical error, and FDA meant to state that'pregnancy registries should be established ". ..as early as possible after a new product is approved."

The second paragraph mentions the concept of comparative registries of old and new products. There is no discussion regarding the rationale for such registries, and we question whether this would be a scientifically valid approach, given the inherent biases regarding enrollment of patients taking older products vs. those taking newer products. PhRMA recommends that this section should either be

bolstered with an appropriate rationale and supporting **data,** or deleted **altogether.**

Is there a scientific rationale for recommending a heterogenous population? Although this could allow analysis of various demographic subgroupings, it is **highly** unlikely that sufficient numbers of pregnant patients could be recruited to detect statistically significant differences between the groups.

We agree with the idea that pregnancy registries should include both domestic and international data. In fact, we urge FDA to review and revise the entire guidance document to include a more international perspective, especially with regard to patient privacy and confidentiality implications.

VI. WHAT DOES A WELL-DESIGNED REGISTRY LOOK LIKE?

A, **Background** Information – A balance needs to be drawn between providing details to non-specialist health care providers beyond what is in the product labeling versus providing the product labeling itself. In addition, this section devotes only one sentence to a very significant concept in understanding the data that derive from a registry, that of the impact of the medical condition being treated on the pregnancy outcome. Assembling this information is often quite difficult, yet the idea is presented in the guidance document without any emphasis on the importance of this information in evaluating overall risk, or in defining a comparative group, if one is to be used.

The third paragraph details requirements for estimates of various populations that might be exposed to the drug. It is nearly impossible to provide a reasonably reliable estimate of the amount off-label use, the number of women of child-bearing potential or the number of pregnant women who will be exposed to a new product before the product is launched. The value of including this information in the protocol is unclear.

B. Description of Research Methods – In the first paragraph of the Patient *recruitment* subsection, the draft guidance suggests that **patients** will usually be recruited via notices in the product labeling, notices in promotional materials, and information on the Internet. **PhRMA** believes that recruitment strategies are the responsibility of the sponsor; therefore, it is improper to suggest that all of these various strategies will be used routinely for all products.

The second paragraph in this section mentions that the study protocol should include' registry information that will be used for registry announcements, to recruit patients into the registry, and to answer questions from health care professionals and patients. We question whether the protocol is an appropriate place for this information, and also have concerns regarding providing information that is not included in the'producf labeling to patients through registry documents. Most questions directed to the registry would probably involve requests for data on outcomes of pregnancies in patients exposed to the product, and other information not available at the time the protocol is written. The third paragraph in this subsection states that ". . . all such materials should be discussed with and reviewed by the appropriate new product review division or office at FDA and the Division. of Drug Marketing and Communication..." Does this refer only to promotional materials containing information about the pregnancy registry, or all mentions of the registry? PhRMA asserts that FDA does not have the regulatory authority to request prior review of such materials by DDMAC. Rather, a sponsor must satisfy the regulatory requirements of 21 CFR 314.81 and submit materials with Form FDA 2253, as appropriate.

The last two paragraphs in this subsection describe collection of data through health care providers versus collection of the data from the patients themselves. The tone of this discussion leaves the impression that patient-reported registries are better than physician-reported registries, when in fact, both types of registries have positive and negative aspects. Direct recruitment of consumers may be problematic for industry from a liability perspective. In addition, member companies' experience in this area indicates that some countries (France, for example) do not allow companies to obtain informed consent for follow-up of pregnancies directly from patients, but require consent to be obtained through the patient's health care provider. For some patient populations (e.g., HIV-infected women) it is virtually impossible to use a patient-reported registry, due to factors such as the transient nature of the population, lack of motivation to participate in medical research unless it perhaps involves access to investigational medication, etc. In addition, in the best of circumstances, this type of registry is-extremely labor-intensive and therefore, expensive to conduct. This section also suggests that collecting pregnancy information from health care providers-and obtaining informed consent are mutually exclusive. On the contrary, one can obtain patient consent through the health care provider, and thus have permission to obtain medical records from both prenatal and pediatric providers. It is preferable that the guidance document refrain from providing judgments regarding which approach to a registry is better. Instead, the guidance document should state

that the sponsor should examine all the-alternatives, and determine the appropriate methodology, based on the patient population involved, the suspected risk of the medication in pregnancy; the number of patients to be enrolled, etc.

Although the last sentence in this subsection mentions that the question of whether all pregnancy registries require informed consent and Institutional Review Board review is "unsettled," the previous sentence states that the informed consent form and protocol "should be cleared" by an IRB. Since pregnancy registries are observational in nature, and these types of programs generally are not reviewed by IRBs, what is FDA's rationale for requiring IRB review for pregnancy registries?

Eligibility requirements -- The first sentence requires some clarification. It states ". . . should be enrolled...after exposure to a product prior to and/or during pregnancy.. ." which could be interpreted to mean that women should be enrolled in the registry after exposure but prior to pregnancy. This would require enrolling all women of childbearing potential as soon as the product was prescribed. This is certainly not feasible, and is probably not what FDA intended.

The first paragraph in this subsection states that reports received after prenatal testing are usually considered retrospective. Member companies' experience with existing pregnancy registries indicates that experts in this field feel that there is enough lack of sensitivity and specificity in the various prenatal tests that reports received after prenatal testing can be included with prospective reports if the prenatal tests did not identify an abnormality. In addition, this paragraph mentions that limiting enrollment to women recruited during the first trimester may help reduce certain biases. We recommend deleting this statement, since data on exposure to drugs at various stages prior to or during pregnancy are useful. An appropriate study design and analysis plan should be used to minimize-any potential biases.

The last paragraph in this subsection states that retrospective reports. identified during the recruitment process are considered to be spontaneous reports. These reports are **not** spontaneous reports. They are collected during active recruitment of the patient into the registry, and thus should be considered solicited reports, as outlined in FDA's "Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Clarification of What to Report," August 1997, pages 3-4. Under this guidance, solicited reports are to be reported as information

obtained from a postmarketing study, and only submitted to FDA if they involve serious, unexpected events which are related to the drug. This interpretation of the solicited reports guidance has also been confirmed by FDA staff to at least one member company, specifically in response to a question concerning retrospective reports to a pregnancy registry. PhRMA objects strongly to FDA requiring each sponsor of a registry to individually request a waiver from spontaneous reporting of retrospective pregnancy registry reports – this would just institutionalize the vague and inconsistent reporting situation that currently exists. Instead, PhRMA urges FDA to establish reasonable expedited and periodic safety reporting requirements for both prospective and retrospective reports from pregnancy registries that could be followed consistently by all sponsors.

PhRMA also recommends that all discussion of regulatory reporting requirements be combined into a single section of the guidance document (e.g., a subsection of VII. Reporting Results).

Data collection at *enrollment* – Although earlier in the document FDA states that the question of informed consent is still unsettled, the first sentence of this subsection makes it sound like informed consent is a requirement. PhRMA recommends that this phrase be deleted. The data collection requirements outlined in the draft guidance document (collection of a large amount of data, including exposures to environmental and behavioral factors, as well as data on ". . . a spectrum of conditions.. . ranging.. . to trivial") give the impression that a single pregnancy registry can study everything related to pregnancy. Data collected should be consistent with the research questions of interest. Collecting data on many characteristics, even if it were possible to obtain valid, reproducible data on such things as measures of environmental. and behavioral exposures or on "trivial" outcomes, without a clear rationale, increases the likelihood that spurious relationships will be found or results will be obtajned that are difficult to interpret. A better approach is to define the research question (e.g., increased risk of major birth defects among pregnancies with first trimester exposure), collect data on characteristics for which there is some rationale to believe they may be confounders or explanatory variables, and collect outcome data on the major fetal events that are of interest. More extensive data can be collected post hoc should the target of interest occur. This section should also stress the importance of obtaining contact information at enrollment, as this is essential to collecting complete follow-up information.

Patient follow-up – This section is written in a manner that assumes the sponsor will always recruit the patient directly, and must follow-up with the patient throughout the pregnancy. This approach may not be appropriate for all pregnancy registries. Registry design is the responsibility of the 'sponsor, and not all registries will use the same design. This section also mentions that registries might collect more complete follow-up information if the names and contact information are available for "close friends and relatives" of the patient. This is a particularly troublesome recommendation, given current concerns about patient privacy (not to mention the privacy of the patient's friends and relatives). This guidance must also be considered in light of the international aspects of pregnancy registries, and international regulations concerning privacy and confidentiality. It would be preferable for the guidance to simply encourage sponsors of each registry to incorporate appropriate approaches (in concert with local laws and advice from Institutional Review Boards as appropriate) to facilitate as complete a collection of follow-up data as possible on each patient.

Study Outcomes – This section again seems to imply that a pregnancy registry can be used to study any and all pregnancy-related outcomes, including maternal adverse events. As mentioned above, data collection should be consistent with the research questions of interest, which may or may not include maternal adverse events. The fourth paragraph in this subsection lists various methods that may be used to collect information on pregnancy outcome. This is fine; however, the listed methods are joined with "and," implying that all methods must be used in every registry. This sentence should be revised to indicate that these methods are available to the sponsor, who is free to choose those best suited to the specific registry.

The statements regarding more in-depth follow-up appear to suggest that registries should support additional testing which may or may not be routinely conducted during the course of routine clinical care. This can lead to detection of subclinical events, etc., and if not directed by a hypothesis being tested, could result in spurious associations-of product risk. As noted earlier, pregnancy registries are observational in nature. Any intervention (e.g., additional diagnostic testing) must be done in the context of a study, not a surveillance system.

Selection of a comparison group – This entire section is particularly troublesome. As discussed earlier, the draft guidance document seems to be alternatively describing a pregnancy registry to collect information on specific drug/biologic exposures, and a cohort study that enrolls women exposed to a

certain product during pregnancy and a comparative non-exposed cohort. The impression given is that concurrent comparison groups are always necessary (although how these women can be encouraged to enroll in a registry is not discussed, and would certainly be a challenging objective). Registries typically do not have concurrent internal comparison groups; comparisons are mostly to external rates; One of the comparison groups described in the document implies that pregnancy risks have been quantified for many products, specifically other products to treat the same indication. This is rather unlikely.

In many diseases such as HIV and other serious, life-threatening diseases that are differentially distributed in populations, it is extremely difficult to find an appropriate comparison group. For most diseases that require treatment during pregnancy, it is impossible to find a population of untreated controls, For studies involving HIV infected patients, historical untreated controls are inappropriate due to changes in overall care of these patients, and it is difficult to find contemporary untreated controls. Women treated with antiretrovirals other than the drug under study are not appropriate because of potential class effects and selection issues. Friends and neighbors are not appropriate for obvious reasons. Comparison to general population rates is more appropriate in the absence of good data in untreated pregnant women with the same disease. An appropriate control group does not ameliorate potential referral bias.

ICH has recently released for consultation a Step 2 document on Topic E10, Choice of Control Groups in Clinical Trials. Although this document focuses on clinical trials, not registries, consideration should be given to including it as a reference in the guidance document.

Statistical considerations - The alternative hypothesis should be clearly stated. Since one of the primary objectives is to show the-exposed group is not worse (non-inferior) than the comparison group, instead of the Type I, error, the sample size may be derived based on an acceptable limit for the confidence interval of the treatment difference. The. acceptable limit for "non-inferiority" should be specified in the protocol.

Methods of data analysis - The discussion regarding stratification could be clearer. The document emphasizes the value of prospective reports over retrospective, since prospective reports provide the most unbiased data to the registry. Given this premise, cases should first be stratified by prospective and retrospective status, before stratification by pregnancy

outcomes. The various levels of stratification specified might not be possible, given the amount of data available. The document should indicate that the amount of analysis is dependent on the data; one can do more with more data. The description of survival data analysis should be more clearly stated, In addition to the 95% confidence interval for each proportion, the 95% CI for the difference of the treatment groups should be reported.

VII. REPORTING RESULTS

As mentioned previously, PhRMA recommends that discussion of regulatory reporting requirements under 21 CFR 314.80 (expedited and periodic) be included in a separate subsection within this section of the draft guidance.

FDA has not addressed reporting of adverse events from pregnancy registries either by regulations or guidances, and guidance provided by FDA to various sponsors has been inconsistent. Guidance is definitely needed in this area; however, the draft guidance document does more to add to the confusion than to ameliorate it. On one hand, FDA states that pregnancy registries are post-marketing studies, while on the other hand they state that adverse events reported in these registries should be treated as spontaneous reports. These reports are definitely not spontaneous in nature, and PhRMA fails to understand FDA's rationale for requiring reporting as if they were. The draft guidance document also mentions that sponsors may seek waivers from these reporting requirements if they so desire.

As an active surveillance program, a pregnancy registry is not strictly speaking a "postmarketing study," unless it is structured to evaluate an *a priori* hypothesis. This distinction is significant for several reasons, including:

- The degree of depth and focus of data collection varies if a registry is for the purpose of hypothesis generation vs. hypothesis testing.
- It is generally not necessary, or even feasible, to include a comparison group in a surveillance system such as a pregnancy registry. A comparison group can be defined more clearly once a specific hypothesis is developed for testing.

On the other hand, reports from pregnancy registries are not spontaneous reports either, since the information is collected through planned contacts and active solicitation of information from patients and/or health care providers, and is not spontaneously reported to the sponsor.

PhRMA strongly objects to this approach, which will only institutionalize the vague and inconsistent reporting situation that currently exists. Instead; PhRMA urges FDA to establish reasonable expedited and periodic reporting requirements for both prospective and retrospective reports from pregnancy registries, requirements that can be followed consistently by all sponsors.

PhRMA recommends that the guidance document be revised to clearly state that reports from pregnancy registries are considered to be solicited reports, and that reporting of adverse events from these registries should follow the reporting guidance outlined in FDA's August 1997 guidance document, which states that solicited reports are to be reported as information obtained from a postmarketing study. Those regulations [21 CFR 314.80(e)(l)] require expedited reporting for serious, unexpected events for which the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience. This guidance document should also clarify that adverse events identified through pregnancies reported retrospectively to the registries are also considered solicited reports, and should follow the reporting guidance outlined in the August 1997 guidance document. This interpretation of the solicited reports guidance has also been confirmed by FDA staff to at least one member company, specifically in response to a question concerning retrospective reports to a pregnancy registry.

Postmarketing study reports (and therefore, solicited reports) are not subject to current Periodic Reporting requirements, except to list and summarize the expedited reports that have been submitted during the reporting period. It is recognized that FDA will introduce requirements for Periodic Safety Update Reports (PSURs) along the lines of ICH E2C guidelines, and any data resulting from pregnancy registries would be included in such PSURs.

The statement "Exceptions are when the sponsor is not involved in the registry and when adverse event reporting is not required by FDA.. ." is not clear. Does this refer to exposure to OTC products marketed under monographs (which are not reportable at the present time)? If the applicantis aware of a registry, although it is not funding it or otherwise supporting it, should the applicant have access to these data? If such an applicant does receive reports from a registry, what are the applicants obligations regarding reporting? If a registry sponsor receives a report of an adverse pregnancy outcome involving another (non-registry sponsor) applicant's product, what are the registry sponsor's regulatory reporting responsibilities? It is unclear from the draft guidance document what should be done in these circumstances.

The discussion of interim, annual, and final registry reports (paragraphs 2 through 4 of this section) also needs some clarification. Methods arid frequency of reporting should be described in the registryprotocol. Unless there are changes to the methods, there is no need to repeat them in interim and annual reports. For many registries, annual reporting'of results should be sufficient; however, for some, semiannnual reporting maybe more appropriate. Whaf timeframes did FDA have in mind for interim reports? In addition, depending on the design of the registry, there may not be a "final report of pregnancy registry findings;" for example, if the registry is designed to continue through most, if not all, of the product's market lifetime.

The list of items identified as "minimal" data to include in interim reports is quite extensive, and not all elements are relevant to all registries. PhRMA recommends that this section of the draft guidance document be rewritten to identify as "minimal data" only those items that are truly applicable to all pregnancy registries. Other data items should be described, but the draft guidance document should make it clear that these elements should be included in interim reports only if relevant to the specific registry. Also, the proportion of spontaneous abortions should be stratified by when reported (week reported), not by when occurred.

VIII. OTHER CONSIDERATIONS AND ADDITIONAL STUDIES

The first paragraph in this section focuses a bit strongly on referral bias. The guidance document should elaborate on what is meant by "referral bias," and what impact it might have on results. Although it cannot be completely eliminated, enrollment of exposed patients as early in their pregnancy as possible can minimize referral bias. This requires education of both patients and health care providers.

The second paragraph in this section discusses using automated HMO and Medicaid databases for additional studies to confirm and follow-up findings of concern identified from pregnancy registries. This section should include additional information about the use of these databases. At a minimum, references about using databases for pharmacoepidemiologic studies should be cited, as well as references that describe the advantages and limitations of such studies. No discussion is provided, for example, about the need to have access to the original medical records for validation and confirmation, which is critical to these types of studies. In addition, it is often very difficult to find sufficient pregnancy exposure data in automated databases unless the drug is extremely widely used, especially for newly approved products.

Attachment 1 - Suggested Data Elements for Pregnancy Registries

Noticeably absent from this list is some sort of patient identifier (name, initials, chart number, etc.). This is essential to be able to conduct follow-up activities, and to identify and avoid duplicate reports.

The list of data elements is quite extensive; in fact, if the primary contact is the patient, it is doubtful that the level of detail specified in the guideline could be collected. Even for health care providers, requiring this level of detail would be a disincentive for participating in the registry. These elements should be identified as items to consider collecting in a pregnancy registry, not "suggested minimal data elements." That said, one additional piece of information that could be useful in evaluating pregnancy registry data is the method of conception (e.g., naturally, in *vitro* fertilization, GIFT, etc.).

Attachment 2 - Sample Size Determinations for Studies of Adverse Pregnancy Outcomes

This table suggests that >10,000 exposed pregnancies are needed to detect moderately common birth defects such as clubfoot. In terms of both cost and length of time to recruit such numbers of patients (and an equal number in any comparison group), these figures are prohibitive for most products and manufacturers.

Additional Items Not Addressed in the Draft Guidance Document

1. Although reference is made throughout the draft guidance to the use of registry data for product labeling, it is unclear how normal pregnancy outcome findings will be used, The product label may not be the most appropriate place for information about pregnancies without adverse effects, but data on normal pregnancy outcomes. following drug exposure are equally important to medical care providers and their patients.

2. Paternal risk factors - The draft guidance document makes no reference to paternal risk factors during data collection, selection of a comparison group, or in causality assessment. Any analysis of risk to pregnancy outcomes should include both parents, especially in instances when there is known to be an increased risk of abnormal offspring due to paternal factors such as advanced paternal age or drug use. In addition, the draft guidance document does not touch upon instances where a pregnancy risk may occur from

paternal, rather than maternal, exposure to the drug under study. This is a **very complex** issue'; **however, it might** be desirable to mention this topic in the guidance document, even if just to state that it is outside the scope of the document.

3. Registries sponsored by more than one company - The draft guidance document does not address the situation where a pregnancy registry for a given disease is sponsored by multiple companies. There are several such existing registries, and because there are both scientific and economic advantages to establishing a small number of relatively large registries (vs. a large number of small registries), this phenomenon is likely to increase. Since issues that have arisen in existing multi-company registries have primarily involved regulatory reporting requirements, PhRMA suggests that this issue be addressed in the Reporting Results section of the guidance document. Wherever it is addressed, PhRMA urges FDA to address this issue in the guidance document.

4. The draft guidance is silent with respect to drug substances that are present in multiple formulations. In such a case, PhRMA suggests that adequate information on the drug substance should be the usual objective (rather than collection of information on each and every formulation).

Thank you for the opportunity to comment on this important matter.

Sincerely,

Michael J. Horan

Michael J. **Horan,** M.D., **Sc.M.**